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Pharmacokinetics of Intravenous Cefetamet and Oral Cefetamet Pivoxil in Patients with Renal Insufficiency

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The pharmacokinetics of cefetamet after a short intravenous infusion of cefetamet (515 mg) and oral administration of 1,000 mg of cefetamet pivoxil were studied in 9 healthy subjects and in 38 patients with various degrees of renal impairment. The results showed that cefetamet elimination was dependent on renal function. After intravenous dosing, total body (CL_S), renal (CL_R), and nonrenal (CL_{NR}) clearances were linearly related to creatinine clearance (CL_{CR}; r = 0.95, 0.92, and 0.59, respectively). Elimination half-life ($t_{1/2\beta}$) was prolonged from 2.46 ± 0.33 h in normal subjects to 29.1 ± 13.9 h in patients with CL_{CR} of <10 ml/min per 1.73 m^2. Correspondingly, CL_S and CL_R decreased from 1.77 ± 0.27 and 1.42 ± 0.25 ml/min per kg to 0.14 ± 0.04 and 0.04 ± 0.03 ml/min per kg, respectively. The volume of distribution at steady state (0.298 ± 0.049 liter/kg) for cefetamet was not altered by renal insufficiency ($P > 0.05$). After oral administration, the elimination parameters, $t_{1/2\beta}$ and CL_R, were insignificantly different from the intravenous data ($P > 0.05$). Furthermore, the bioavailability (F) of cefetamet pivoxil (45 ± 13%) was not altered by renal failure ($P > 0.05$). However, maximum concentration in plasma and the time to achieve this value were significantly increased (5.86 ± 0.74 versus 14.8 ± 6.14 μg/ml and 3.9 ± 1.1 versus 8.4 ± 1.7 h, respectively; $P < 0.05$). Based on these observations, it is recommended that patients with CL_{CR} of <10 ml/min per 1.73 m^2 and between 10 and 39 ml/min per 1.73 m^2 be given one-quarter of the normal daily dose either once or twice daily. Patients with CL_{CR} between 40 and 80 ml/min per 1.73 m^2 should receive one-half of the normal dose twice daily. For patients with CL_{CR} of <10 ml/min per 1.73 m^2, it would be recommended that they receive a normal standard dose as a loading dose on day 1 of treatment.

Cefetamet pivoxil is the prodrug (pivaloyloxymethylester) of a new broad-spectrum cephalosporin antibiotic, cefetamet. This compound possesses a broad spectrum of antimicrobial activity against many aerobic gram-positive and gram-negative organisms (19). Previous pharmacokinetic studies in normal healthy volunteers revealed that the low-protein-bound (22%) cefetamet is mainly eliminated by the kidneys via glomerular filtration (2, 12). This kinetic behavior is similar to that of other β-lactam antibiotics with low protein binding and high urinary recovery (e.g., carumonam [11], ceftizoxime [1, 15], and ceftazidime [1, 15]). Consequently, the pharmacokinetics of cefetamet are expected to be dependent on changes in renal function.

The objectives of this study were to determine the pharmacokinetics of cefetamet and cefetamet pivoxil after intravenous and oral administration to patients with various degrees of impaired renal function, to compare these results with those obtained from healthy volunteers who have normal renal functions, and to determine dosage guidelines for patients with renal impairment.

MATERIALS AND METHODS

Subjects. Nine healthy volunteers (7 men and 2 women) and 38 patients (22 men and 16 women) with various degrees of impaired renal function were recruited from four study centers (University Medical Outpatient Department, Bern, Switzerland [3 healthy volunteers, 10 patients]; Department of Medicine, University of Freiburg, Freiburg, Federal Republic of Germany [3 healthy volunteers, 11 patients]; Division of Nephrology, Laiko General Hospital, Athens, Greece [15 patients]; Community Hospital of Baden-Baden, Baden-Baden, Federal Republic of Germany [3 healthy volunteers, 2 patients]).

These subjects were categorized arbitrarily into four groups according to their measured 24-h creatinine clearances (CL_{CR}): group 1, subjects with normal renal function (CL_{CR}, >80 ml/min per 1.73 m^2); group 2, subjects with mild renal insufficiency (CL_{CR}, 40 to 80 ml/min per 1.73 m^2); group 3, subjects with moderate renal failure (CL_{CR}, 10 to 39 ml/min per 1.73 m^2); and group 4, subjects with severe renal failure (CL_{CR}, <10 ml/min per 1.73 m^2). The demographic characteristics of these groups are given in Table 1.

The study was approved by the institutional ethical committees of the participating centers. Written informed consent was obtained from all subjects before enrollment in the study. Before and after completion of the study, each subject underwent a complete physical examination, a 12-lead electrocardiogram, and a series of laboratory tests (hematology, blood chemistry, and urinalysis). Subjects with abnormal biochemical parameters, with the exception of creatinine, were excluded from participation in this study. Additional exclusion criteria included any history of drug hypersensitivity, anemia out of proportion to the degree of renal insufficiency, and hepatic or cardiovascular disease. Heavy smokers (>10 cigarettes per day) were excluded from participation. In healthy normal volunteers, no prescription

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TABLE 1. Demographic characteristics of healthy subjects and patients with various degrees of renal insufficiency

Group	No.		Mean ± SD (range)			
	Males	Females	Age (yr)	Wt (kg)	Surface area (m^2)	CL_{CR} (ml/min per 1.73 m^2)
1	7	2	37 ± 18 (22–68)	74 ± 12 (60–96)	1.88 ± 0.12 (1.71–2.00)	99 ± 14 (84–126)
2	9	3	53 ± 14 (22–68)	74 ± 12 (55–93)	1.86 ± 0.15 (1.59–2.12)	62 ± 9.4 (50–77)
3	6	9	56 ± 16 (31–80)	69 ± 15 (43–97)	1.77 ± 0.22 (1.37–2.05)	22 ± 10 (11–38)
4	7	4	56 ± 9 (46–72)	67 ± 10 (48–82)	1.76 ± 0.14 (1.50–1.97)	5.1 ± 3.0 (1.1–9.6)

medication was allowed within 14 days and no over-the-counter medication was allowed within 3 days prior to the initiation of the study. If concurrent medication was absolutely necessary in a renal disease patient, the prescribed drug(s) had to be listed on the case report forms with the exact dosage schedule. Patients with severe renal impairment on hemodialysis were studied in the interval between two dialyses.

Study design. Each subject received the following two treatments in a randomized crossover fashion at intervals ranging from 4 to 14 days: a short (3- to 5-min) intravenous infusion of 545 mg of cefetamet monosodium salt (equivalent to 515 mg of cefetamet free acid) or two 500-mg cefetamet pivoxil tablets (equivalent to 700 mg of cefetamet free acid) with 150 ml of water. Before the second treatment, the drug levels in urine and plasma of all subjects were below the limit of detection. In each instance, the drug was administered 5 min after completion of a standard breakfast.

The subjects fasted from 10 p.m. the evening prior to dosing. Cefetamet pivoxil was given with 150 ml of water 5 min after a standard breakfast. Four hours following drug administration, the subjects were given a standard light lunch. Venous blood and urine samples were collected immediately before and at appropriate time intervals up to 24 (group 1), 36 (group 2), 74 (group 3), and 98 (group 4) h after dosing. The same procedures as described in our previous reports (2, 12) were used for blood and urine collection and sample handling and storage.

Analytics. Cefetamet was determined in plasma and urine by a high-performance liquid chromatography method (20). A 24-hour creatinine clearance was obtained during the first 24-h interval after each drug treatment. Creatinine in serum and urine was analyzed by the method of Helger et al. (10).

Lower limits of quantification for cefetamet in plasma and urine were 0.5 and 20 μg/ml, respectively. Interassay reproducibilities were 4.1 to 6.2% in plasma and 3.6 to 4.7% in urine.

Pharmacokinetic analysis. Following oral administration, the maximum concentration of cefetamet (C_{max}) and the time to achieve this concentration (T_{max}) were read directly from the concentration-versus-time curves.

Plasma concentration data were analyzed by standard model, independent pharmacokinetic techniques. Terminal elimination rate constants (β) were estimated for all curves by performing standard unweighted linear least-square regression analysis of the linear segment of the log concentration-versus-time data. The slope of this line is equal to $-\beta$. The area under the plasma concentration-versus-time curve (AUC) was estimated by using a combination of the linear and log trapezoidal rules (6). The log trapezoidal rule was used when concentration data were in an exponentially declining phase. The AUC from the last point to infinity was estimated by dividing the last concentration by β.

The $t_{1/2\beta}$ was estimated by dividing 0.693 by β. Systemic clearance (CL_S) following the intravenous dose was estimated by dividing the dose by the $AUC_{0-\infty}$. Renal clearance (CL_R) was calculated by dividing the total amount of cefetamet excreted in the urine by the corresponding AUC.

Nonrenal clearance (CL_{NR}) was determined by subtracting CL_R from CL_S. The volume of distribution at steady state (V_{SS}) was obtained by the standard statistical moments theory (6). The absolute bioavailability (F) of the tablets was estimated as the dose-corrected $AUC_{0-\infty}$ ratio. The total urinary recovery of cefetamet (f_u) was calculated as the percentage of dose regained during the time intervals 0 to 24 (group 1), 0 to 36 (group 2), 0 to 72 (group 3), and 0 to 96 (group 4) h.

Statistics. Group differences (sex, age, weight, C_{max}, T_{max}, $AUC_{0-\infty}$, V_{SS}, F, f_u, $t_{1/2\beta}$, CL_S, CL_R, and CL_{NR}) were tested by the Kruskal-Wallis test. For significant test results, subsequent multiple Mann-Whitney U tests were performed and interpreted on an unaltered significance level similar to Fisher's least-significant-difference procedure for multiple comparisons in the case of normally distributed values (14). The level of significance was set at 0.05. Simple linear regression analysis was used to correlate CL_S, CL_R, and CL_{NR} with CL_{CR}.

RESULTS

Both oral cefetamet pivoxil and intravenous cefetamet were generally well tolerated. However, there were two reports of headache in two healthy subjects and one incidence of mild diarrhea in a patient from group 4 after cefetamet pivoxil administration. In addition, a second patient in group 4 complained about dizziness and heartburn after cefetamet pivoxil. With the exception of creatinine serum concentrations, the biochemical parameters in all subjects before and after completion of the study were within the normal range. The four groups of subjects participating in the study (Table 1) were comparable in sex,

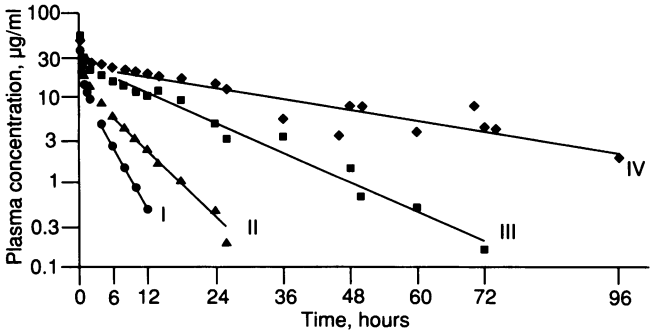

FIG. 1. Mean plasma concentration-time profiles of cefetamet after intravenous administration of 545 mg of cefetamet monosodium salt (equivalent to 515 mg of cefetamet free acid) to groups 1, 2, 3, and 4.

TABLE 2. Pharmacokinetic parameters (means ± standard deviations) of cefetamet after intravenous infusion of 545 mg of cefetamet monosodium salt and after oral administration of 1,000 mg of cefetamet pivoxil

Group (n)	Route of administration[a]	C_{max} (μg/ml)	T_{max} (h)	$AUC_{0-\infty}$ (μg · h/ml)	$t_{1/2\beta}$ (h)	ml/min per kg			V_{SS} (liters/kg)	f_u (%)	F (%)
						CL_S	CL_R	CL_{NR}			
1 (9)	i.v.			67.4 ± 8.2	2.46 ± 0.33	1.77 ± 0.27	1.42 ± 0.25	0.35 ± 0.21	0.299 ± 0.043	80 ± 11	
	p.o.	5.86 ± 0.74	3.9 ± 1.1	41.6 ± 8.3	2.58 ± 0.34		1.48 ± 0.22			38 ± 7.8	47 ± 7.9
2 (12)	i.v.			121 ± 51.6	3.96 ± 1.84	1.23 ± 0.74	0.94 ± 0.56	0.29 ± 0.28	0.296 ± 0.045	77 ± 15	
	p.o.	7.83 ± 2.66	4.1 ± 1.2	77.0 ± 37.2	4.36 ± 1.86		0.88 ± 0.45			34 ± 9.6	47 ± 11
3 (15)	i.v.			385 ± 162	10.8 ± 3.84	0.40 ± 0.19	0.24 ± 0.17[b]	0.16 ± 0.09[b]	0.303 ± 0.057	57 ± 18[b]	
	p.o.	12.3 ± 5.25	4.9 ± 0.7	248 ± 173	10.6 ± 4.17		0.24 ± 0.17			23 ± 8.4	44 ± 15
4 (11)	i.v.			1,077 ± 371	29.1 ± 13.9	0.14 ± 0.04	0.04 ± 0.03[c]	0.09 ± 0.04[c]	0.292 ± 0.052	29 ± 15[c]	
	p.o.	14.7 ± 6.14	8.4 ± 1.7	613 ± 171	28.8 ± 11.7		0.04 ± 0.02[c]			11 ± 5.3[c]	45 ± 15

[a] i.v., Intravenous; p.o., oral.
[b] n = 14.
[c] n = 10.

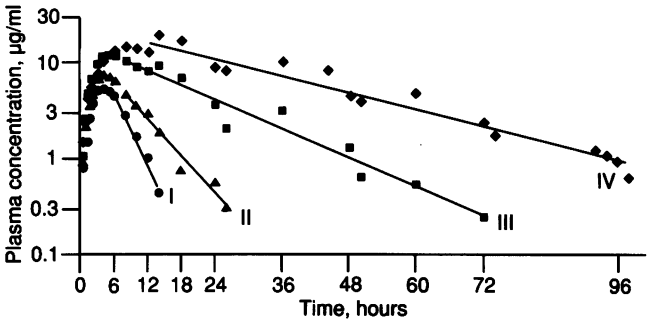

FIG. 2. Mean plasma concentration-time profiles of cefetamet after oral treatment with 1,000 mg (two tablets) of cefetamet pivoxil (equivalent to 700 mg of cefetamet free acid), 5 min after a standard breakfast, in groups 1, 2, 3, and 4.

weight, and body surface area distribution ($P > 0.05$). A significant ($P < 0.05$) difference existed, however, in the age distributions between the healthy volunteers (group 1) and the patient population (groups 2, 3, and 4).

Intravenous infusion. Figure 1 shows the semilogarithmic plots of mean cefetamet plasma concentration-versus-time data after a short (3- to 5-min) intravenous infusion of 545 mg of cefetamet monosodium salt (equivalent to 515 mg of cefetamet free acid) to subjects in groups 1 to 4. The concentrations of cefetamet in plasma declined in all four groups in a biphasic fashion, whereby the rate of decline during the postdistributive stage decreased considerably with declining renal function. CL_S, CL_R, and CL_{NR} were linearly related to creatinine clearance (r = 0.95, 0.92, and 0.59, respectively).

Mean pharmacokinetic parameters for groups 1 to 4 are summarized in Table 2. With declining renal function, there were significant increases in $AUC_{0-\infty}$ (67.4 to 1,077 μg · h/ml) and $t_{1/2\beta}$ (2.46 to 29.1 h) and significant declines in CL_S (1.77 to 0.14 ml/min per kg), CL_R (1.42 to 0.04 ml/min per kg), CL_{NR} (0.35 to 0.09 ml/min per kg), and f_u (80 to 29%). While all comparisons among the four different groups were statistically significant for $AUC_{0-\infty}$, $t_{1/2\beta}$, CL_S, and CL_R, no significant difference could be detected for either CL_{NR} or f_u between groups 1 and 2 or, in addition, for CL_{NR} between groups 2 and 3. No significant influence of renal impairment on V_{SS} was found.

Oral administration. Figure 2 shows the semilogarithmic plots of mean cefetamet plasma concentration-versus-time data after oral administration of 1,000 mg of cefetamet pivoxil 5 min after a standard breakfast to subjects in groups 1 to 4. Consistent with intravenous data (Fig. 1), the terminal slope of cefetamet following oral administration decreased with declining renal function. This resulted in markedly higher 12-h concentrations of cefetamet in plasma of patients from group 4 (12.7 ± 4.85 μg/ml) compared with patients from group 1 (1.00 ± 0.55 μg/ml). Table 2 summarizes the mean pharmacokinetic parameters obtained from these plasma concentration-versus-time plots. With declining renal function, there were significant differences between groups 1 and 4 in T_{max} (3.9 to 8.4 h), C_{max} (5.86 to 14.7 μg/ml), $t_{1/2\beta}$ (2.58 to 28.8 h), $AUC_{0-\infty}$ (41.6 to 613 μg · h/ml), CL_R (1.48 to 0.04 ml/min per kg), and f_u (38 to 11%).

On the other hand, no significant difference was observed for F. An inspection of the individual group comparisons showed that all comparisons were significant for $AUC_{0-\infty}$, CL_R, and $t_{1/2\beta}$, but not for C_{max} (no significance between groups 3 and 4), T_{max} (no significance between groups 1 and 2 or 2 and 3), and f_u (no significance between groups 1 and 2).

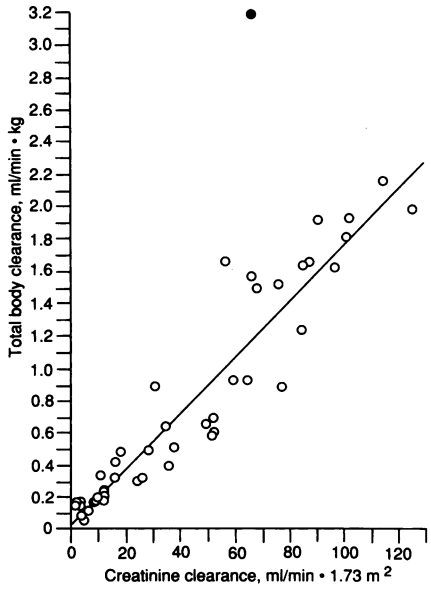

FIG. 3. Correlation between total body clearance (CL_S) of cefetamet and creatinine clearance (CL_{CR}) after a short intravenous infusion of 545 mg of cefetamet monosodium salt (equivalent to 515 mg of cefetamet free acid): $CL_S = 0.017 \times CL_{CR} + 0.028$; $r = 0.95$. One point (●) was treated as outlier and not used for the linear regression analysis.

DISCUSSION

Cefetamet belongs to the group of β-lactam antibiotics with low protein binding, limited nonrenal elimination, and primary renal excretion by glomerular filtration (15). The elimination of this group of compounds, e.g., ceftizoxime and ceftazidime (13), is directly dependent on renal function. Cefetamet is no exception. This relationship is indicated in Fig. 3 and 4, which show that CL_S and CL_R are linearly related to CL_{CR}.

In addition to the changes in CL_R, CL_{NR} also appears lower with declining renal function. Reduced CL_{NR}s with declining renal function have been reported for β-lactam antibiotics such as cefsulodin (8), carumonam (11), cefixime (9), and ceftriaxone (16). The mechanism(s) responsible for this decline in CL_{NR} has not been elucidated for β-lactam antibiotics that are primarily eliminated unchanged. Decreases in hepatic clearance due to decreases in drug-metabolizing enzyme activities in acute or chronic renal failure patients are, on the other hand, well known (4, 7, 18). Usually, when the relationship between CL_S and CL_{CR} is examined by linear regression, it is assumed that the ordinate intercept is an estimate of CL_{NR}. However, since CL_{NR} decreases with CL_{CR} in our subjects (Table 2), the ordinate intercept in Fig. 3 does not reflect the CL_{NR} value in group 1. The relationship between CL_S and CL_{CR} is actually nonlinear. Nevertheless, there was an overall strong linear correlation ($r = 0.95$) between CL_S and CL_{CR} (Fig. 3), and for all practical purposes this correlation is adequate for the design of clinical dose adjustments of cefetamet pivoxil (see below).

Changes in the distribution characteristics of acidic drugs in uremic patients are mainly dependent on alterations in plasma protein binding (3, 17). Marked effects can, however, only be expected with extensively plasma-protein-bound drugs (>90%) (17). Since cefetamet is not highly bound to plasma proteins (22%) (12), it is not surprising that the V_{SS} of cefetamet remains unchanged in patients with renal failure. There is little information in the literature relating to the

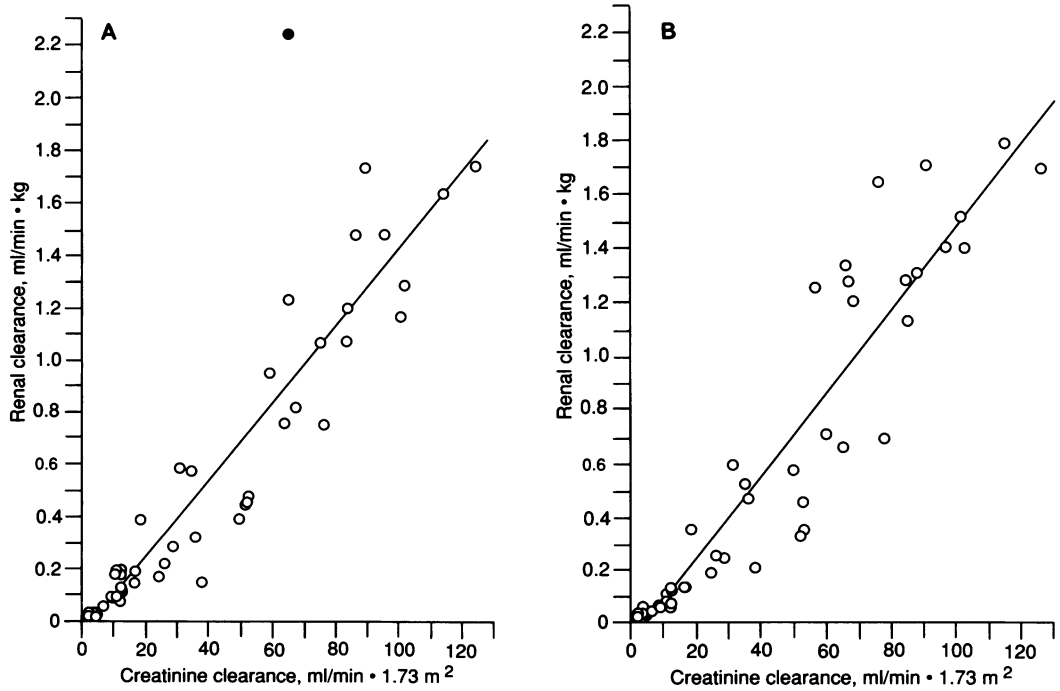

FIG. 4. Correlation between renal clearance (CL_R) of cefetamet and creatinine clearance (CL_{CR}). (A) After a short intravenous infusion of 545 mg of cefetamet monosodium salt (equivalent to 515 mg of cefetamet free acid), $CL_R = 0.015 \times CL_{CR} - 0.059$; $r = 0.92$. One point (●) was treated as outlier and not used for the linear regression analysis. (B) After 1,000 mg of oral cefetamet pivoxil (equivalent to 700 mg of cefetamet free acid), $CL_R = 0.016 \times CL_{CR} - 0.076$; $r = 0.94$.

modifications of absorption characteristics of cephalosporins in renal failure. Our results clearly showed that the absolute bioavailability of cefetamet pivoxil is not changed in renal failure (Table 2), suggesting that the overall absorption mechanisms are not affected. Also, there seems to be no relevant difference in esterase activity between healthy normal volunteers and renal disease patients. C_{max} and T_{max} are increased in renal failure patients (Table 2). This increase is not related to an increase in cefetamet pivoxil absorption but rather to a reduction in the elimination of the drug. It is well known that C_{max} and T_{max} are determined by both absorption and elimination parameters (6). The difference in age between our healthy normal volunteers (group 1) and the renal disease population should not have influenced our data. An age effect on the kinetics of cefetamet has been shown to be secondary to a reduction in renal function. Advanced age has not been shown to have an influence on the bioavailability or V_{SS} of cefetamet (2).

Based on the results of the present study, it is apparent that, if normal dosages of cefetamet pivoxil were given to patients with reduced renal function, significant accumulation of the drug would occur during multiple dosing. To maintain similar average steady-state concentrations of cefetamet in plasma of patients with compromised renal function, the dosing interval or dose could be adjusted according to the following formula (3, 11): $(\tau_N/\tau_R\ [D = \text{constant}]) = (D_R/D_N\ [\tau = \text{constant}]) = [(0.017 \times CL_{CR} + 0.028)/1.77]$, where τ_N and τ_R and D_N and D_R are the dosing interval and the dose of cefetamet pivoxil in subjects with normal and compromised renal function, respectively. The numerator $0.017 \times CL_{CR} + 0.028$ represents the regression line from Fig. 3, and the constant 1.77 is the mean value of CL_S in normal subjects (Table 2).

The optimal dosage adjustment is based on the mathematical relationship described above, the size of tablets available, and convenience. It is recommended that the longest τ be set at 24 h for reasons of compliance. For a standard dosage, which is 1,000 mg of cefetamet pivoxil taken every 12 h, it is recommended that patients with mild renal failure (group 2) take half of the recommended dose every 12 h.

Patients with moderate renal insufficiency (group 3) would take 250 mg of cefetamet pivoxil every 12 h, whereas patients with severe renal failure (group 4) would receive 250 mg of the drug once daily. Generally, it takes four to five half-lives to reach steady-state concentrations. To avoid the possibility of subtherapeutic concentrations at the onset of treatment (in patients with severe renal impairment [group 4]), we recommend starting treatment with a standard dosage of 1,000 mg of cefetamet pivoxil (loading dose).

By using the mean pharmacokinetic parameters obtained from the four groups of subjects (Table 2), computer simulations were performed to generate plasma concentration-versus-time profiles according to recommended dosage guidelines. Predicted steady-state C_{max} and C_{trough} in patients with normal renal function were 5.7 and 0.4 μg/ml, respectively. In contrast, patients with severe renal impairment would be expected to have steady-state C_{max} and C_{trough} of 7.5 and 6.0 μg/ml. These simulated results suggest that the peak steady-state concentration is increased slightly in renal failure. However, renal failure will produce marked elevation in trough cefetamet concentrations despite dosage reduction. Since clinical efficacy of β-lactam antibiotics correlates positively with the time (unbound) concentrations in plasma spent above the bacterial MIC (5, 19), the efficacy of cefetamet should not be altered in renal failure patients who use our dosage guidelines. At the same time, the tolerability should not be affected, since cefetamet has, like other β-lactam antibiotics, a wide therapeutic margin.

In summary, the absorption of cefetamet pivoxil and distribution of cefetamet are not affected by renal failure. However, the elimination of cefetamet is directly related to CL_{CR}. A dosage guideline is proposed for patients with various degrees of renal impairment.

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